1808-118
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
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SCOTT CROWE et al.)
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Serial No. 07/952,640) Examiner: C. Eisenschenk
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Filed: December 1, 1992) Group Art Unit: 1806
)
For: PRODUCTION OF ANTIBODIES)

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Alan Lewis, declare that:

1. I am the same Alan Lewis named as an inventor on the above-referenced patent application.

2. I received my B.Sc. Honors Degree in Biological Sciences in 1984 and my Ph.D in 1987 from the University of Leicester. From 1987-1990 I conducted postdoctoral research in molecular biology at Wellcome Biotech. Since 1990, I have been employed as a molecular biologist in the department of cell biology at the Wellcome Research Laboratories. In this position, my work has focused on carrying out fundamental research in immunochemistry using recombinant DNA technology for the purpose of formulating new therapeutic antibody molecules. A copy of my curriculum vitae is attached.

3. I have read and understand the Office Action issued by the U.S. Patent and Trademark Office on May 27, 1994, in connection with this patent application. In paragraph 18 of the Action, the examiner asserted that claims 1-14, all of the claims pending in the application, stand rejected under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure is not enabling for the use of the claimed invention as a diagnostic aid. More specifically, the examiner stated that the specification does not teach how to use the antibodies made in accordance with the claimed invention as diagnostic aids.

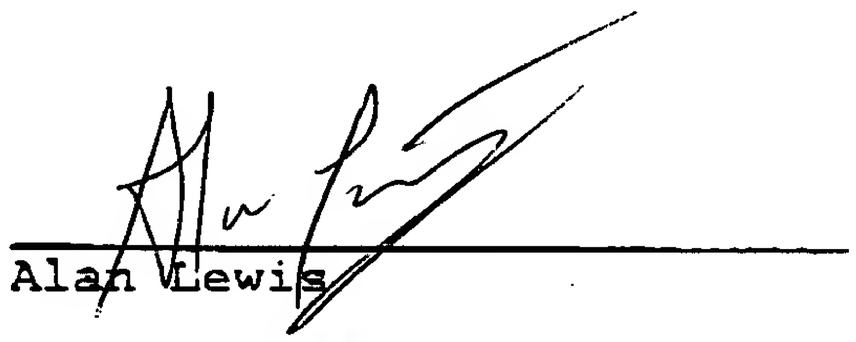
4. This application discloses and claims a process for the production of a recombinant primate antibody. As used in this application, "primate" encompasses humans, apes, old world monkeys, new world monkeys and prosimians. The process of the invention comprises selecting a cell line derived from a primate lymphocyte that is capable of expressing a desired antibody, isolating RNA from that cell line and separating mRNA from the other isolated RNA, synthesizing cDNA from the mRNA and inserting that cDNA into a cloning vector, transforming a host cell with the vector containing the cDNA in order to obtain a library, screening the library for cDNA which encodes the constant and variable regions of the heavy and light chains of the desired antibody, inserting that cDNA encoding the heavy and light chains into an expression vector, and then culturing the transfected host cell under antibody-producing conditions and then isolating the desired antibody.

5. Persons of ordinary skill in the art of immunology will be able to use the recombinant primate antibodies of this invention in various diagnostic assays absent specific instructions for doing so. Specifically, one of skill in the art could replace in a radioimmunoassay (RIA) or an enzyme linked immunosorbent assay (ELISA) the currently used antibody which specifically recognizes a particular antigen with a recombinant primate antibody made in accordance with the teachings of this invention which specifically recognizes that antigen. As these immunoassay techniques are based upon the specific interaction of the antibody with the antigen to provide information about antigenic specificity, the recombinant antibody can be used interchangeably with the hybridoma-produced antibody. Producing the antibody recombinantly as taught in this application does not alter the antibody's ability to bind to the antigen.

6. For example, two diagnostic assays presently on the market include the Wellcozyme™ anti-HAV (hepatitis A virus) immunoassay (VK34) and the HIV (Immunodeficiency Virus) immunoassay (VK56/57), both of which are presently marketed by Murex Diagnostics. Both assays are ELISA assays which utilize a specific anti-viral antibody conjugated to the enzyme horseradish peroxidase to measure the quantity of either anti-HAV antibody or anti-HIV antibody present in serum samples using a standard competitive binding assay. A recombinant primate antibody prepared by the process taught in the present application from a lymphocyte cell line expressing a functional antibody with a

desired specificity for HAV or for HIV easily could be substituted for the HAV or HIV antibodies presently used in these commercial assays. Such a substitution would require no more than routine experimentation to establish that the assay utilizing the recombinant primate antibodies of the present invention functioned reproducibly in the assay.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Alan Lewis

30/10/96

Date

PUBLICATION LIST
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Lewis. A.P. and Brookfield. J.F.Y. (1987) Movement of *Drosophila melanogaster* transposable elements other than P elements in a P-M hybrid dysgenesis cross. Mol. Gen. Genet. 208:506-510.

Brookfield. J.F.Y. and Lewis. A.P. (1989) Somatic reversion of P transposable element insertion mutations in the *singed* locus of *Drosophila melanogaster* requiring specific P insertions and a *trans*-acting factor. Genet. Res., Camb. 54:101-112.

Lewis. A.P. (1989) The 230000 molecular mass merozoite surface antigen of *Plasmodium yoelii*: cloning and analysis of the 3' half of the gene. J. Cell. Biochem. 13E:142.

Lewis. A.P. (1989) Cloning and analysis of the gene encoding the 230-kilodalton merozoite surface antigen of *Plasmodium yoelii*. Mol. Biochem. Parasitol. 36:271-282.

Lewis. A.P. (1990) Sequence analysis upstream of the gene encoding the precursor to the major merozoite surface antigens of *Plasmodium yoelii*. Mol. Biochem. Parasitol. 39:285-288.

Keen. J., Holder. A., Playfair. J., Lockyer. M. and Lewis. A. (1990) Identification of the gene for a *Plasmodium yoelii* rhoptry protein. Multiple copies in the parasite genome. Mol. Biochem. Parasitol. 42:241-246.

Lewis. A.P. and Crowe. J.S. (1991) Immunoglobulin complementarity-determining region grafting by recombinant polymerase chain reaction to generate humanised monoclonal antibodies. Gene 101:297-302.

Lewis. A.P., Parry. N., Peakman. T.C. and Crowe. J.S. (1992) Rescue and expression of human immunoglobulin genes to generate functional human monoclonal antibodies. Hum. Antibod. Hybridomas. 3:146-152.

Gewert. D., Salom. C., Barber. K., Macbride. S., Cooper. H., Lewis. A., Wood. J. and Crowe. S. (1993) Analysis of interferon-α2 sequences in human genomic DNA. J. Interferon Res. 13:227-231.

Lewis. A.P. and Crowe. J.S. (1993) Generation of humanized monoclonal antibodies by 'best fit' framework selection and recombinant polymerase chain reaction. In: Terhorst. C., Malavasi. F. and Albertini. A. (eds.), Generation of Antibodies by Cell and Gene Immortalization. Year Immunol. Basel. Karger, vol 7. pp. 110-118.

Sims. M.J., Hassal. D.G., Brett. S., Rowan. W., Lockyer. M.J., Angel. A., Lewis. A.P., Hale. G., Waldmann. H. and Crowe. J.S. (1993) A humanized CD18 antibody can block function without cell destruction. J. Immunol. 151:2296-2308.

Lewis. A.P., Lemon. S.M., Barber. K.A., Murphy. P., Parry. N.R., Peakman. T.C., Sims. M.J., Worden. J. and Crowe. J.S. (1993) Rescue, expression. and analysis of a neutralizing human anti-hepatitis A virus monoclonal antibody. J. Immunol. 151:2829-2838.

Lewis. A.P., Barber. K.A., Cooper. H.J., Sims. M.J., Worden. J. and Crowe. J.S. (1993) Cloning and sequence analysis of κ and γ cynomolgus monkey immunoglobulin cDNAs. Developmental Comp. Immunol. 17:549-560.

Crowe. J.S., Gewert. D.R. Barber. K.A., Lewis. A.P., Sims. M.J., Davies. S.L., Salom. C.L., Wood. J., Thomas. H.C., Thursz. M. and Lok. A.S. (1994) Interferon (IFN)-α2 genotype analysis of Chinese chronic hepatitis B patients undergoing recombinant IFN-α2a therapy. J. Infect. Dis. 169:875-878.

Lewis, A.P., Sims, M.J., Gewert, D.R., Peakman, T.C., Spence, H. and Crowe, J.S. (1994) *Taq* polymerase extension of internal primers blocks polymerase chain reactions allowing differential amplification of molecules with identical 5' and 3' ends. Nucleic Acids Res. 22:2859-2861.